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Predictive factors for postoperative outcome in temporal lobe epilepsy according to two different classifications

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Summary

Purpose: The determination of prognostic factors is important for predicting outcome after epilepsy surgery. We investigated the factors related to surgical outcome within a homogeneous group of patients suffering from pathologically proven mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), and compared Engel's outcome classification system with the latest one proposed by the ILAE.
Method: We included 109 patients with MTLE-HS who were followed-up for at least 1 year after epilepsy surgery. A retrospective chart review was performed to extract patients' demographic details, and potential pre-postoperative risk factors. Outcome of surgery was defined by the Engel's and ILAE classifications. In addition, the course of prognosis was determined according to the changes in ILAE classifications on an annual basis. Univariate and multivariate logistic regression analyses were used for the latest available outcomes and two different courses of prognosis.
Results: The average duration of follow up was 4.78 ± 2.55 years in the 109 patients with MTLE-HS. The univariate and multiple logistic regression analyses showed that the occurrence of seizures during the first month after surgery was a significant risk factor for a poor outcome. A history of trauma was also significant for patients with late recurrence of postsurgical seizures after at least 1-year seizure remission.

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Conclusion: The occurrence of seizures during the first month after surgery is a significant prognostic factor in patients with MTLE-HS. Ignoring early postoperative seizures in classification systems may result in difficulty in identifying the course of epilepsy after surgery.

Introduction

The rate of complete remission of seizures after epilepsy surgery for temporal lobe epilepsy was reported as 68–85%.[1] Almost one third of patients continue to have seizures after surgery. The outcome in the long term is worse than that in the short term and 48–55% of patients did not become seizure-free more than 5 years after the operation.[2–4] Therefore, the determination of prognostic factors for epilepsy surgery is important for the counselling of patients in everyday practice.

Several previous studies have reported predictive variables of outcome after epilepsy surgery but most have included a variety of temporal lobe pathologies including indeterminate findings and normal or nonspecific abnormality,[5–7] some have no pathological data,[8,9] and some have included both temporal and extratemporal cases.[6,7,10] Mesial temporal lobe epilepsy (MTLE) pathologically characterized by hippocampal sclerosis (HS) is the prototype for surgically remediable epileptic syndromes.[11] There have been few studies of the prognostic factors within this subgroup of patients with MTLE-HS.[12–17] To the best of our knowledge, only four studies have examined the outcome of surgery in a homogeneous group with MTLE-HS that was defined histopathologically.[12,14,15,17]

Another problem in most previous studies about outcome after epilepsy surgery is the use of different methods of classification and cross-sectional analysis of outcomes during different time periods. The calculation of the proportion of patients who are seizure-free for some years after surgery provides only a snapshot of cohort outcomes during that period. The cross-sectional method of analysis may be problematic as the correlation of variables with outcome may yield different results depending on the stage of the postoperative course at which outcome was assessed.[2] To avoid this problem, we examined outcome in a group with MTLE-HS for the whole follow-up period in each patient, in addition to the last available outcome. The last available outcome of each patient was also defined using both Engel's outcome classification[18] and the new ILAE classification.[19]

We investigated the factors related to surgical outcome within a group of pathologically proven MTLE-HS patients, comparing the two classification systems. Besides we also tried to determine how postoperative prognosis was altered by time.

Methods

All patients who received surgical treatment for intractable temporal lobe seizures at our center between 1995 and 2006 were reviewed for possible inclusion in the study.

Presurgical evaluation and patient selection

A detailed clinical history was obtained from patients considered possible candidates for epilepsy surgery. Resistance to first-line anti-epileptic drugs (AED) was evaluated. As a rule, high-resolution brain magnetic resonance (MR) imaging was performed. With most patients, MR images were obtained using either 1.5 or 3.0T scanners (Symphony and Allegra, respectively, Siemens, Erlangen, Germany). The MR imaging protocol performed for patients with epilepsy in our institution includes coronal 3D T1-weighted (W) gradient-echo imaging (MPRAGE) obtained parallel to the brainstem, and fluid-attenuated inversion recovery (FLAIR), and T2-W turbo spin-echo and T1-W inversion recovery images obtained perpendicular to the hippocampi in addition to routine brain imaging. A 32-channel EEG recording system was used. Scalp electrodes including T1–T2 electrodes were placed according to 10–20 systems. Patients underwent continuous video-EEG monitoring lasting 3–10 days. Findings from presurgical evaluations were discussed at a multidisciplinary case conference, where decisions were made concerning the possibility and type of surgery. For patients in whom hippocampal sclerosis was present on imaging, an operation was performed when interictal and ictal EEG findings were concordant with MR imaging. Our standard procedure for treating MTLE was anterior temporal lobectomy with removal of the medial structures including the amygdala, hippocampus and parahippocampal gyrus. We performed standard anterior temporal lobe resection in all patients. We resected 3,5 cm of lateral temporal lobe from the anterior temporal tip for the dominant hemisphere and 5 cm for the nondominant one. Patients who underwent epilepsy surgery were re-examined every 6 months after that, with an assessment of the seizure outcome as well as an evaluation of the psychiatric and social status. Our protocol is for patients to receive AEDs for a minimum of 2 years post-operatively. The type of AEDs may change or the dosage may decrease after 1 year. Two years after successful surgery, the option of complete AED discontinuation is tailored to the individual patient.

This study included 109 patients who were followed-up for at least 1 year and who had HS shown on MR imaging and confirmed by postoperative pathological analysis. The hippocampal subfields and dentate gyrus were examined for neuronal loss and gliosis by visual analysis. Hippocampal sclerosis was defined as more than 50% neuron loss in the CA1 subfield.

Data collection

A retrospective chart review was performed to extract patients' demographic details, and potential preoperative and postoperative risk factors. The following variables were investigated: gender; presence of mental retardation; age at epilepsy onset (onset of habitual seizures, excluding febrile seizures); presence of family history and consanguinity of parents; history of natal or perinatal injury as perinatal risk factors; histories of febrile seizures, trauma and status epilepticus, aura; history of secondarily generalized tonic-clonic seizures (SGTCS); number of AEDs used before surgery; age at operation; duration of epilepsy; interictal scalp electroencephalographic findings (EEG); follow-up periods; presence of surgical complications; frequency of postoperative seizure days on an annual basis on each anniversary of the surgery and usage of AEDs for each postoperative year. The annual and latest available seizure outcomes of patients described in detail using both the classification system of Engel's Classes I—IV[18] and the new ILAE classification system Classes 1—6.[19] Seizures occurring in first postoperative month were ignored in classifications. We also looked at the occurrence of seizures within the first 2 days and first month (between days 3 and 30). It has been suggested that acute early seizures within a few days, mostly in the first 48 h after surgery may be less prognostically important because this is when the acute surgical effects like electrolyte imbalance, hypoxia, hypoglycemia or hypocapnia are the most pronounced and the risk of a low AED level is frequent.[18,20] Because of that seizure outcome for the first 2 days were not included in the first month outcome. Patients' previous medical charts were reviewed and the missing variables were ascertained by asking the patients and their relatives. The location and frequency of interictal epileptiform discharges were assessed by visual analysis of interictal EEG samples. Unilateral interictal epileptiform discharges were defined if at least 70% of interictal discharges appeared over one temporal lobe. The detailed ictal EEG findings of these patients will be reported in a parallel study that is currently being performed.

Outcome assessment

At each visit, the information collected included seizure frequency, medication intake and compliance, and the effect of seizures on daily activities or social status. Neuropsychological outcomes were not included. To minimize the lack of contribution to outcome determination, we obtained the latest information by telephone calls in 94 patients. Outcome of surgery was defined according to the Engel's and ILAE classifications.[18,19] Outcome status was determined every year for up to 11 years after surgery by outpatient clinical interview or telephone interview. Patients were categorized as seizure-free (Engel's Class I or ILAE Class 1 or 2) or not (Engel's Classes II—IV or ILAE Classes 3—5). Also the patients who were completely free from both seizures and auras[21,22] at the last available outcome (ILAE Class 1a which corresponds to Engel's Class IA) were determined. Fifteen patients who could not be contacted by outpatient or telephone interview were categorized according to their medical charts at their last follow-up year.

Furthermore, the changes in ILAE classification that occurred on an annual basis were documented graphically for each patient, except for 4 patients (n = 105) who were followed-up for a year only. In patients with changes in outcomes, it was attempted to isolate clinical characteristics related to specific patterns such as the running down (RD) phenomenon (becoming seizure free after some early postoperative seizures) or the reverse form of it (late seizure recurrence after an initial, at least 1 year, seizure free period).[23,24]

Statistical methods

An independent samples t test was used for continuous variables: age at operation, age at epilepsy onset (onset of habitual seizures), epilepsy duration before surgery (defined by the difference between age at operation and age at onset), number of drugs used before surgery, follow-up period in months and seizure frequency per month before surgery.

A Chi-square or Fisher's exact test of independence was used for univariate analysis of the following categoric variables: gender, side of surgery, presence of mental retardation and perinatal risk factors, presence of family history and consanguinity of parents, histories of febrile seizures, trauma, status epilepticus, presence of aura, history of SGTCS before surgery, presence of ipsilateral interictal

Table 1 Clinical features of 109 patients with TLE-HS

	n/total		Mean±SD
Gender			
Male	42/109		
Side of surgery			
R	58/109		
Handedness			
R	92/109		
L	11/109		
Bilateral	6/109		
Age at onset of habitual seizures (yr±SD)			9.64±6.53
Age at surgery (yr±SD)			28.14±7.55
Preoperative duration of epilepsy			18.55±7.78
Follow up period (month)			52.28±30.75
Year			4.00±2.57
Remnant time (month)			4.40±3.28
No of drugs used before surgery			2.43±1.49
History of febrile seizure	73/109		
History of trauma	43/109		
History of perinatal-natal injury	20/109		
History of epilepsy in family	47/109		
Consanguinity of parents	21/109		
History of status epilepticus	23/109		
History of SGTCS	66/109		
History of aura	97/109		
EEG			
IE on iiEEG	96/100		
Surgical complication	22/109		
Infection	3		
Subdural-epidural hematoma	4		
Transient cranial nerve palsy	6	22	
Transient hemiparesia	5		
Permenant hemiparesia	1		
Others	3		
No of patients with postoperative seizures (except during first month)	46/109		
Initial seizure recurrence at 1st year	21		
2nd year	13		
3rd year	3	46	
4th year	7		
5th year	1		
8th year	1		
No of patients with seizures at first month after surgery	11/109		

IE, ipsilateral epileptiform abnormality; iiEEG, interictal EEG.

epileptiform discharges on interictal EEG and presence of surgical complications.

Backward stepwise multiple logistic regression analysis was used to assess the prognostic importance of the clinical variables. Odds ratios (ORs) were calculated for each surgical outcome group: Engel's Class I and others (Classes II–IV), and ILAE Classes 1 and 2 and others (Classes 3–5). Multivariate analysis was performed on variables that were $p < 0.15$ in the univariate analysis.

Results

The present study included 109 patients with medically intractable seizures who underwent temporal lobe resection in whom pathological examination of the excised material revealed HS and who were followed-up for at least 1 year.

Tables 1 and 2 show details of the clinical and outcome findings. Of the 109 patients 67 (61%) were female. The mean age at surgery was 28.14 ± 2.55

Table 2 Last available outcome of patients after surgery

	N	%
Engel's Classification (n=109)		
Engel's IA	48/90	83
IB	19/90	
IC	21/90	
ID	2/90	
Engel's IIA	4/17	16
IIB	3/17	
IID	10/17	
Engel's IIIA	2/2	1
ILAE Classification (n=109)		
Class 1	82/109	75
Class 2	10/109	9
Class 3	3/109	3
Class 4	13/109	12
Class 5	1/109	1
Course of prognosis (n=105[a])		
Stable	52/105	50
Running down (RD)	23/105	22
Late recurrence[b]	12/105	11
Transient worsening	16/105	15
Transient improvement	2/105	2

[a]The changes in ILAE classification occurred on annual basis (course of prognosis) were documented for each patient, except 4 who were followed up for a year only.
[b]Late seizure recurrence after an initial, at least 1 year, seizure free period.

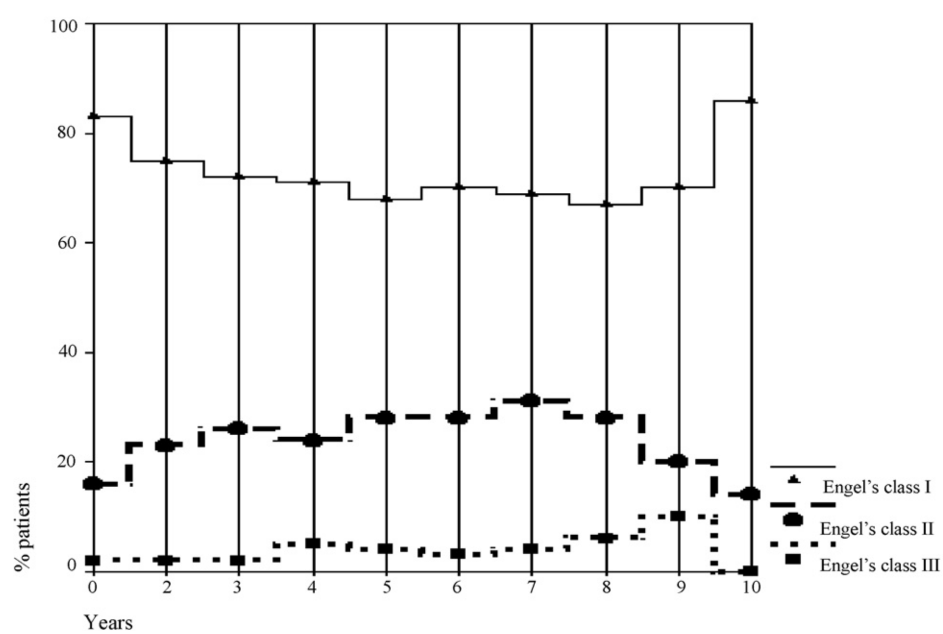
years (range 15—52 years). The age at epilepsy onset ranged from 7 to 32 years (mean 9.64 ± 6.53 years). The mean epilepsy duration was 18.55 ± 7.78 years. The average duration of follow-up was 52.28 ± 30.75 months or 4.78 ± 2.55 years (1—11 years). The mean number of AEDs used before surgery was 2.43 ± 1.49. In 51 patients, the resection was on the left side (47%) and in the other 58 it was on the right.

Interictal EEG reports of 100 patients were available in their charts. In 96 patients interictal EEG showed ipsilateral epileptiform discharges. Surgical complications were reported in 22 (20%) of 109 patients, but only one had a major complication. Ninety-four patients (86%) were reevaluated by telephone interview. During the follow-up period, one patient committed suicide. The other reasons why patients were lost to follow-up are unknown.

During the follow-up period, changes in outcome were observed in 53 out of 105 patients who were followed up for more than 1 year. The other 52 patients had a stable course. The RD phenomenon occurred in 23/53 patients (all were in ILAE Classes 1 and 2, at last available outcome; i.e. good prognosis). 12/53 patients who had seizure recurrence after an initial postsurgical seizure free state of at least 1 year, were in ILAE Classes 3—5, at last available outcome (i.e. poor prognosis). Fluctuation of outcomes with transient worsening (16/53) or transient improvement (2/53) was found in the remaining 18 patients.

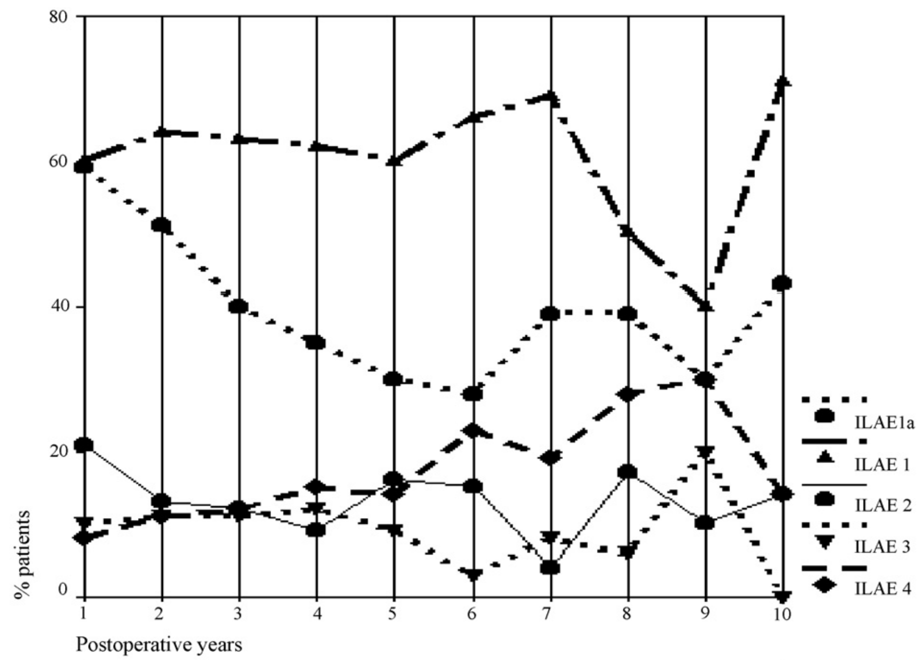
The last available outcome in 90 patients was Engel's Class I, while it was Classes II—IV in 19. With the ILAE classification, the last outcome in 92 patients was Classes 1 and 2 and Classes 3—5 in 17. The seizure-free rate in the last follow-up year was 83% according to Engel's classification (Engel's Class I) and 84% according to the ILAE classification (ILAE Classes 1 and 2). But only 44% of patients (48/109) were completely free from both seizures and auras (Engel's Class IA—ILAE Class 1a) at last available outcome. The year-by-year analysis of surgical outcomes by using Engel's classification and ILAE classification are presented in Figures 1 and 2. Also the comparison of the course of all patients with Engel's Class I and with Engel's Class IA or ILAE Class 1a are shown in Figure 3. From a total of 109 patients 90 (83%) fit the criteria of Engel's Class I at 1 year after surgery, 59/82 (72%) at 3 years after operation, 18/26 (69%) at 7 years after surgery and 6/7 (86%) patients at 10 years after surgery. When patients were classified according to Engel's Class IA or ILAE Class 1a (seizure and aura free) 64/109 (59%) fit the criteria at 1 year, 33/82 (40%) at 3 years, 10/26 (39%) at 7 years and 3/7 (43%) patients at 10 years after surgery.

The AED discontinuation rate after surgery was 24/109 (22%). Other seizure-free patients (Engel's



Total number of patients in each year	1	2.	3	4	5	6	7	8	9	10
	109	105	82	66	57	40	26	18	10	7

Figure 1 Year-by-year seizure outcome based on Engel's classification. Numbers in lower boxes indicate the numbers of patients in the given follow up years.



Total number of patients in each year	1	2.	3	4	5	6	7	8	9	10
	109	105	82	66	57	40	26	18	10	7

Figure 2 Year-by-year seizure outcome based on ILAE classification. Numbers in lower boxes indicate the numbers of patients in the given follow up years.

Class I or ILAE Classes 1 and 2) continued the AEDs. Mean time of discontinuation of AEDs after surgery was 2.83 ± 0.70 years.

Fifty-seven (52%) of the 109 patients had at least one seizure during the entire postoperative follow-up. Eleven (19%) of these 57 experienced their initial seizure recurrence during the first month, 21 (37%) during the first year, and 13 (23%) during the second year. Three (27%) of the 11 patients who had seizures during the first month had no further seizures after that.

Univariate analyses

Table 3 shows the results of univariate analyses of identifying variables between patients with good (ILAE Classes 1 and 2 and Engel's Class I) and poor (ILAE Classes 3—5 and Engel's Classes II—IV) outcome at last follow up. The demographic characteristics were similar among different outcome groups.

The presence of preoperative risk factors including the presence of mental retardation; histories of febrile seizures, trauma, infection, status epilepticus; and the presence of seizures during sleep; aura and SGTCS were not associated with a poor prognosis at last available outcome. Interictal EEG findings with scalp electrodes and the presence of surgical complications did not predict the surgical outcome. Resections on the left side did not differ from those on the other side in terms of surgical outcome.

Univariate analysis revealed that the presence of seizures during the first month (3—30 days) after surgery was a significant risk factor for postsurgical outcome in the last follow-up period. During the first month after surgery, 6/19 patients in Engel's Classes II—IV ($p = 0.004$) and 5/17 patients in ILAE Classes 3—5 ($p = 0.01$) had recurrence of seizures (Table 3).

After the findings about the significance of the seizures during first month, some features of 11 patients who had seizures during the first month were re-evaluated. Five of these patients were classified as seizure free (Engel's Class I) and 6 of them were not seizure free at the last available outcome. Seizures in the first month (3—30 days) occurred mostly after a week from the surgery. The exact day of these seizures could not be obtained in eight patients. The number of seizures changed from 1 to 4 times for each patient during that period, totally 24 seizures were reported for all 11 patients. Seizures of 7 patients were resembling the habitual preoperative seizures in mild form but features of seizures were not described in 4 patients. All of the patients used their AEDs regularly during these periods but AEDs serum levels were not noted at these times. Furthermore preoperative electrophysiological and neuroradiolo-

Table 3 Univariate analysis of the variables between groups which include Engel's Class I and Engel's Classes II, III, IV or new classification of ILAE Classes 1 and 2 and Classes 3—5 at last outcome

	Engel's Class I (*n* = 90)	Engel's Classes II—III—IV (*n* = 19)	—	ILAE Classes 1 and 2 (*n* = 92)	ILAE Classes 3—5 (*n* = 17)	*p*
Age at surgery (year; mean ± S.D.)	27.73 ± 7.51	30.05 ± 7.63	0.22	27.81 ± 7.43	29.88 ± 8.14	0.30
Duration of epilepsy (year; mean ± S.D.)	17.79 ± 7.26	21.94 ± 9.49	0.39	17.90 ± 7.36	21.58 ± 9.38	0.07
Duration of epilepsy >20 years	31/90	11/19	0.06	32/92	10/17	0.10
Site of surgery (right temporal)	50/90	8/19	0.32	52/92	6/17	0.10
Gender (male)	36/90	6/19	0.60	35/92	7/17	0.79
Marital status (married)	20/90	5/19	0.76	20/92	5/17	0.53
Right handed	78/90	14/19	0.15	80/92	12/17	0.13
Presence of mental retardation	18/90	5/19	0.53	19/92	4/17	1.0
First seizure at the age of ≥6 years old	22/90	2/19	0.23	22/92	2/17	0.35
Presence of family history	39/90	8/19	1.00	42/92	5/17	0.29
Presence perinatal risk factors	15/90	5/19	0.34	17/92	3/17	1.00
History of trauma	34/90	9/19	0.60	33/92	10/17	0.11
History of febrile seizures	60/90	13/19	1.0	63/92	10/17	0.57
Consanguinity of parents	18/90	3/19	1.0	19/92	2/17	0.52
Recurrent seizures at the age of ≥6 years	63/90	9/19	0.10	63/92	9/17	0.25
History of status epilepticus	18/90	5/19	0.53	18/92	5/17	0.52
History of SGTCS	53/90	13/19	1.0	55/92	11/17	0.79
Presence of aura	80/90	17/19	1.0	81/92	16/17	0.68
IE abnormality on iiEEG	80/84	16/16	1.0	82/86	14/14	1.0
Complication of surgery	21/90	1/19	0.11	21/92	1/17	0.18
Presence of seizure at first month	5/90	6/19	0.004	6/92	5/17	0.01
Withdrawal of antiepileptics after surgery	23/90	1/19	0.07	22/92	2/17	0.35

IE, ipsilateral epileptiform abnormality; iiEEG, interictal EEG.

gical findings of these 11 patients with seizures during the first month after surgery were re-evaluated. All of the patients except one had unilateral interictal epileptiform discharges (more than >80%) on the side of operation. Only one patient had 60% ipsilateral interictal epileptiform discharges. Ictal EEG disclosed lateralized temporal rhythmic discharges on the side of surgery in all patients. On MR imaging all patients had unilateral hippocampal atrophy at the side of operation. There were no complications related to surgical procedure during the postoperative period.

Univariate analysis was also performed on these risk factors for patients with RD phenomenon or patients with late postsurgical seizure recurrence who were seizure free at least for a year after surgery. Only history of trauma was significantly different between two groups. Trauma history was present in 21% of those with the RD phenomenon and in 75% of patients in the latter group ($p = 0.003$).

Multivariate analysis

We performed a multivariate analysis for the presence of seizures in the first postoperative month. Standard stepwise multiple logistic regression also showed that the presence of seizures during the first month after surgery was independently predictive for worsening of outcome. (For last available outcome according to Engel's classification: $p = 0.008$ OR = 6.38 95% CI = 1.62–25.13, and for last available outcome according to the new ILAE classification: $p = 0.006$ OR = 0.14 95% CI = 1.76–27.80.) The presence of a history of trauma in patients with late postsurgical seizure recurrence after an initial seizure free period ($p = 0.05$ OR = 0.33 95% CI = 0.003–0.38) was also an independent factor.

Discussion

Seizure outcomes following temporal lobe surgery have been studied extensively in recent years. However, the interpretation of published reports on long-term outcome has been difficult because of several methodological problems.[2] These studies usually use a modified Engel's classification or a new modified form, lacking appropriate standardized classification systems for seizure outcome. In our study, the last available outcomes of each patient were defined as seizure-free or not, according to both worldwide acceptable classification systems, Engel's and the ILAE. Statistical analysis was performed in these two different classification systems. We found that the only predictor of postoperative poor outcome in patients with MTLE-HS shown by univariate and multivariate analysis was recurrence of seizures in the first month after epilepsy surgery in either classification system. Remarkably, no other pre- or perioperative risk factors examined were found to have definite prognostic value in these patients with pathologically proven HS.

The occurrence of early postoperative seizures or auras in the first week after epilepsy surgery is relatively common (up to 49%).[20,25–27] It has been suggested that these early seizures may result from the effects of acute surgical injury and they have been termed neighborhood seizures. Some authors had the opinion that transient neighborhood seizures did not necessarily infer a bad prognosis.[18,19,25] Therefore, in most previous studies of outcome following epilepsy surgery, the early postoperative seizures that occurred during the hospital stay have been ignored. The most commonly used seizure outcome classification[18] is not specific for the time period of early seizures. In 2001, the Commission on Neurosurgery of the ILAE[19] suggested a 4-week period for this.

In the literature, most series showed that in 20–40% of patients with TLE the earliest time period for the risk of recurrence and persistence of seizures was within 6–12 months of surgery.[27–29] However, some previous studies support our findings showing the predictive value of earlier postoperative seizures after TLE surgery on poor prognosis.[4,7,20,23,26,27,30–33] Armon et al. reported that the presence of seizures in 25% of patients within 2 months of surgery was a significant postoperative predictor for poor outcome over 2 years in a heterogeneous group with cortical resections.[7] McIntosh et al. reported that 21.5% of their patients had early postoperative seizures in the first month,[31] and 77% of them experienced subsequent seizures in the first year. They found that patients with early seizures had a risk of seizure recurrence that was almost 3–8 times that of patients without early seizures. They suggested, however, that adjustment of preoperative pathology was important for the prediction of the effect of early postoperative seizures on outcome. The difference in the presence of early seizures rates may be related to the differences in the pathological substrate of the study population and the definition of the early period. Our study was limited to a single pathology MTLE-HS, whereas the earlier studies were not limited. In our homogeneous group of patients with pathologically proven TLE-HS, 10% (11/109) had early seizures between the 3rd and 30th postoperative days, and only 21% of them had no recurrence of seizures after the first month. In our study, involvement of only patients with HS may support the hypothesis that early seizures are a marker for remaining primary or secondary epileptogenesis and intractability of TLE-HS.[33,34] However, further studies with postoperative MR imaging and EEG findings for residual pathology or epileptogenic region in larger numbers of patients are required.

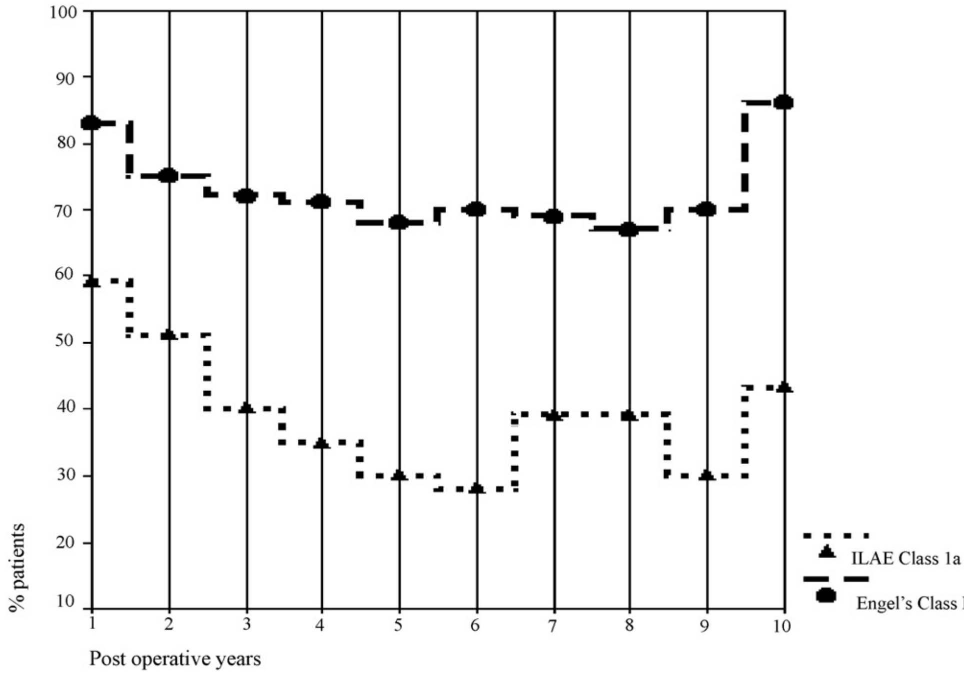
There is a limitation of our retrospective data about features of early seizures like type and timing, and their risk factors such as AEDs serum levels. In the literature, however, the importance of these characteristics of early seizures, which are associated with poor seizure outcome,[4,20,21,23,26,27,31,32] is unclear. Malla et al. reported that patients who had early seizures similar to their preoperative habitual seizures within first month after anterior temporal lobectomy had worse outcome than those with auras, or focal or generalised seizures.[26] However Garcia et al.,[20] found no difference in long term outcomes between patients with postoperative seizures that were similar to preoperative seizures and those seizures different from preoperative seizures. In our study we confirmed that 7 of 11 patients who had early seizures during the first month had seizures similar to preoperative habitual seizures. Five of these 7 patients were classified as poor seizure outcome (Engel's Class II) whereas 1 of 4 patients whose seizure characteristics could not be determined had poor prognosis. In another study, it was suggested that there was a trend toward higher recurrence among patients who experienced a first seizure in the first week rather than in the subsequent 3 weeks after anterior temporal lobectomy with any pathology.[31] Our group of 11 patients with early seizures mostly had seizures after first week but exact time of these were not known.

Contrary to what might be expected, the results related to the significance of other preoperative risk factors were not consistent with the numerous previous studies of the overall group of patients receiving temporal lobe resection for epilepsy. Identified factors that have been shown to predict outcome in these large series include duration of epilepsy,[6,13] age at operation,[5,6,13] history of febrile seizures,[5] concordant interictal epileptiform abnormalities,[9,16,34] and presence of status epilepticus or SGTCS before surgery.[4,15,16] The differences in these predictive factors may be related to the differences in the pathological substrate of the study population. To the best of our knowledge, there are only a few reports that specifically address the surgical outcome of patients with the syndrome MTLE-HS.[12,14–17] In the MTLE subgroup, like in our patients, most of these factors lose their predictive value.

In the literature, very few systematic studies have been performed on patients' natural history and prognostic factors predicting the continued remission of seizures or relapse after surgery.[2] Using only cross-sectional analyses leads to loss of information related to course of prognosis like the running down phenomenon. This approach may also be problematic for correlation of findings depending on the stage of the postoperative period. For that reason, firstly we analysed annual changes in outcome according to the new ILAE classification for each patient. Although the general proportion of seizure-free patients remained stable in our series (52/109), as in the study by Jeong et al. (73/121),[1] some patients showed the RD phenomenon or late seizure recurrence after an initial postsurgical seizure free period in the group with fluctuating course.

The rate of TLE patients with late improvement in postoperative seizure control was reported as 5–44%.[23,24] The RD phenomenon was also observed in 21% (23/109) of our patients. Late seizure recurrence after an initial seizure free period, occurred in 13 of our patients (12%). This type of course was also observed in a few reports.[1,28] There is a suggestion that patients with that course of prognosis who had failed TLE surgery are more likely to have large epileptogenic zones and more diffuse lesions of the type produced by encephalitis and head injury, which often involve the posterior temporal region, and are difficult to eradicate with surgery.[35,36] In support of that we found only the presence of trauma history as a predictive risk factor for late seizure recurrence after an initial seizure free period. This may indicate that changes occur in the functional anatomy of the brain and it becomes susceptible to intractability. However, to the best of our knowledge there is no report related to the clinical details and comparisons of both of these specific outcome patterns. Only Salanova et al. reported that patients with the RD phenomenon were more likely to have a history of febrile seizures, unilateral temporal spiking and almost complete hippocampal resection compared with patients who continued to have seizures.[23] They suggested that a less autonomous residual epileptogenic area causes this clinical phenomenon and runs down over the course of months or years. Future prospective studies that include a large group of patients with a long follow-up period in addition to knowledge about postoperative MR imagings, EEG findings and usage of AEDs would be needed for the analysis of the features of the RD phenomenon or the reverse of that phenomenon, i.e. late seizure recurrence after an initial seizure free period.

In the present study, both classification systems were used for analysis. They have different advantages and disadvantages. Although the 2001 ILAE classification is a modification of Engel's classification, it is more standardized and has more objective criteria. The definitions in the last classification, like frequency of seizures for a year and ratio of seizures according to "baseline seizure days", are more easily applicable. It is useful for annual follow up and for showing the time course of prognosis. In Engel's Class I seizure-free patients are included with those who still have seizures. Although Engel's Class IA refers to absolutely seizure-free patients, like the new classification of ILAE Class 1a, in reality most centers do not report outcomes using Engel's subcategories. Therefore, the actual number of seizure-free patients is frequently obscure.[21,22] In our study when analyses were restricted to Engel's Class IA (or ILAE Class 1a) patients, seizure-aura free ratios were 59% (64/109) and 44% (3/7) at the first and tenth years. However in analyses of Engel's Class I patients, seizure outcome appeared to be better at first year (90/109; 83%) and tenth year (6/7; 86%) follow up, and be more stable with time (Figure 3). But in that stable course we could lose the patients with simple (Engel's Class IB) or dis-



Total number of patients in each year	1	2.	3	4	5	6	7	8	9	10
	109	105	82	66	57	40	26	18	10	7

Figure 3 Year-by-year number of patients with ILAE 1a (Engel's Class IA) and Engel's Class; for comparison of two different definitions of seizure freedom. Numbers in lower boxes indicate the numbers of patients in the given follow up years.

abling seizures (Engel's Class IC) and with seizures related to AED discontinuation (Engel's Class ID). Moreover, the classification of patients having some disabling seizures after surgery (Engel's Class IC) as seizure-free may cause the special course of prognosis like the RD phenomenon to be missed. In the year-by-year reporting of Class 1 outcomes recommended subgroups like "ILAE Class 1a: completely seizure-free since surgery" resembling to Engel's Class IA might be used to indicate the RD phenomenon. Furthermore, recurrence of seizures after more than 1 year seizure-free period might be mentioned for defining the late recurrence of seizures or fluctuating course. In addition, the definition of nocturnal seizures that are less disabling in patient's life is important in classification. However, as these groups of seizures are defined in "seizure days" in the new classification, it could not be specifically mentioned. As a result, the ILAE classification for annual follow up in determination of course of prognosis and Engel's classification for last available outcome may give more realistic results.

The findings of the present study suggest that ignoring early postoperative seizures in both classification systems may result in difficulty in identifying the course of refractory epilepsy after surgery. Early seizures may be a marker for remaining epileptogenesis or intractability in patients with hippocampal sclerosis. They may also show the progressive course of the disease after surgery. The protocol of discontinuation of AEDs or MR imaging follow up after surgery may be reviewed. Moreover, the pathological differences for the functional and anatomical reorganization of limbic structure between children and adults with HS may give information about the chronicity of this disease and may support its progressive form although it was surgically removed.

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